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Our Docket: P-IX 1300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Kauffman and Ballivet

Serial No.: 08/349,510

Filed: December 2, 1994

For: PROCESS FOR OBTAINING DNA, RNA, PEPTIDES, POLYPEPTIDES, OR PROTEIN BY RECOMBINANT DNA TECHNIQUE

Group Art Unit: 1803

Examiner: Moody

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Asst. Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

This Preliminary Amendment is submitted in response to the Office Action mailed June 7, 1994, issued in connection with the parent application to the above-identified application. Applicants respectfully request entry of the following amendments and consideration of remarks below.

Please amend the claims as follows:

Please cancel claims 1-7, 9-17, 23-26, 32-35, 40-44, 57-58, and 65-74 without prejudice and substitute therefor new claims 75 through 119.

Sub G' --75. (New) A method of identifying a peptide, polypeptide or protein having a predetermined binding property, comprising:

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(a) providing a ligand for detecting said predetermined binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences, said polynucleotide sequences encoding a predetermined frequency of two or more amino acid residues at four or more amino acid positions;

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(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins containing said predetermined frequency of two or more amino acid residues at four or more amino acid positions; and

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property.--

--76. (New) The method of claim 75, wherein said two or more amino acid residues further comprises all twenty amino acid residues.--

--~~75~~ 3. (New) The method of claim ~~75~~ 1, wherein said diverse population of stochastically generated polynucleotide sequences, encode at least 10,000 different peptides, polypeptides or proteins.--

--~~78~~ 4. (New) The method of claim ~~75~~ 1, wherein said inserting further comprises hybridization of complementary ends.--

--~~79~~ 5. (New) The method of claim ~~75~~ 1, wherein said inserting further comprises ligation.--

--~~80~~ 6. The method of claim ~~75~~ 1, wherein said diverse population of stochastically generated polynucleotide sequences are produced by stochastic copolymerization of double stranded oligonucleotides.--

Sub G2

--81. (New) The method of claim 75, wherein said diverse population of stochastically generated polynucleotide sequences are produced by copolymerization of the four kinds of nucleotide triphosphates consisting of A, C, G and T.--

--~~82~~ 8. (New) The method of claim ~~75~~ 1, wherein said diverse population of stochastically generated polynucleotide sequences are produced by chemical synthesis.--

--~~83~~ 9. (New) The method of claim ~~75~~ 1, wherein the expression vector is a plasmid.--

--~~84~~ 10. (New) The method of claim ~~83~~ 9, wherein the plasmid is pUC8.--

--~~85~~ 11. (New) The method of claim ~~75~~ 1, wherein the expression vector is viral DNA.--

--~~86~~ 12. (New) The method of claim ~~75~~ 1, wherein the expression vector is a hybrid of plasmid and viral DNA.--

--~~87~~ 13. (New) The method of claim ~~75~~ 1, wherein the expression vector is a phage.--

--88. (New) The method of claim 75, wherein step (c) further comprises digesting the diverse population of expression vectors with a restriction enzyme absent from the expression vector and reinserting the digested products into said digested population of vectors to form a different population having a greater number of new stochastic polynucleotide sequences.--

--89. (New) The peptide, polypeptide, or protein identified by the method of claim 75.--

--90. (New) A method of isolating a polynucleotide sequence encoding a peptide, polypeptide or protein having a predetermined binding property, comprising:

(a) providing a ligand for detecting said predetermined binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences, said polynucleotide sequences encoding a predetermined frequency of two or more amino acid residues at four or more amino acid positions;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins containing said predetermined frequency of two or more amino acid residues at four or more amino acid positions;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property; and

(f) isolating the stochastically generated polynucleotide sequence or sequences which encoding said peptides, polypeptides or proteins having said predetermined binding property.--

--91. (New) The method of claim 90, wherein said two or more amino acid residues further comprises all twenty amino acid residues.--

18 16
--~~92~~. (New) The method of claim ~~90~~, wherein said diverse population of stochastically generated polynucleotide sequences, encode at least 10,000 different peptides, polypeptides or proteins.--

19 16
--~~93~~. (New) The method of claim ~~90~~, wherein said inserting further comprises hybridization of complementary ends.--

20 16
--~~94~~. (New) The method of claim ~~90~~, wherein said inserting further comprises ligation.--

22 16
--~~95~~. The method of claim ~~90~~, wherein said diverse population of stochastically generated polynucleotide sequences are produced by stochastic copolymerization of double stranded oligonucleotides.--

--96. (New) The method of claim 90, wherein said diverse population of stochastically generated polynucleotide sequences are produced by copolymerization of the four kinds of nucleotide triphosphates consisting of A, C, G and T.--

--97. (New) The method of claim 90, wherein step (c) further comprises digesting the diverse population of expression vectors with a restriction enzyme absent from the expression vector and reinserting the digested products into said digested population of vectors to form a different population having a greater number of new stochastic polynucleotide sequences.--

--98. (New) The polynucleotide sequence encoding said peptide, polypeptide, or protein having said predetermined binding property isolated by the method of claim 90.--

--99. (New) A method of isolating a peptide, polypeptide or protein having a predetermined binding property, comprising:

(a) providing a ligand for detecting said predetermined binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences, said polynucleotide sequences encoding a predetermined frequency of two or more amino acid residues at four or more amino acid positions;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors

containing stochastically generated polynucleotide sequences;

(d) expressing said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins containing said predetermined frequency of two or more amino acid residues at four or more amino acid positions;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property;

(f) isolating the stochastically generated polynucleotide sequence or sequences which encoding said peptides, polypeptides or proteins having said predetermined binding property; and

(g) using genetic information from said isolated stochastically generated polynucleotide sequence to produce said peptide, polypeptide or protein having said predetermined binding property.--

--100. (New) The method of claim 99, wherein said two or more amino acid residues further comprises all twenty amino acid residues.--

27 25
--~~101~~. (New) The method of claim ~~99~~, which said diverse population of stochastically generated polynucleotide sequences, encode at least 10,000 different peptides, polypeptides or proteins.--

28 25
--~~102~~. (New) The method of claim ~~99~~, wherein said inserting further comprises hybridization of complementary ends.--

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29 25
--~~103~~. (New) The method of claim ~~99~~, wherein said inserting further comprises ligation.--

30 25
--~~104~~. The method of claim ~~99~~, wherein said diverse population of stochastically generated polynucleotide sequences are produced by stochastic copolymerization of double stranded oligonucleotides.--

Sub G5

--105. (New) The method of claim 99, wherein said diverse population of stochastically generated polynucleotide sequences are produced by copolymerization of the four kinds of nucleotide triphosphates consisting of A, C, G and T.--

32 25
--~~106~~. (New) The method of claim ~~99~~, wherein said diverse population of stochastically generated polynucleotide sequences are produced by chemical synthesis.--

Sub G6

--107. (New) The method of claim 99, wherein step (c) further comprises digesting the diverse population of expression vectors with a restriction enzyme absent from the expression vector and reinserting the digested products into said

digested population of vectors to form a new different population having a greater number of new stochastic polynucleotide sequences.--

--108. (New) The peptide, polypeptide, or protein isolated by the method of claim 99.

--109. (New) A method of producing a diverse population of stochastically generated polynucleotide sequences encoding a diverse population of peptides, polypeptides or proteins having a plurality of different binding properties, comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences, said polynucleotide sequences encoding a predetermined frequency of two or more amino acid residues at four or more amino acid positions; and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.--

--110. (New) The method of claim 109, wherein said two or more amino acid residues further comprises all twenty amino acid residues.--

--~~111~~. 36 (New) The method of claim ~~109~~ 34, which said diverse population of stochastically generated polynucleotide sequences, encode at least 10,000 different peptides, polypeptides or proteins.--

--~~112~~. 37 (New) The method of claim ~~109~~ 34, wherein said inserting further comprises hybridization of complementary ends.--

--~~113~~. 38 (New) The method of claim ~~109~~ 34, wherein said inserting further comprises ligation.--

--114. The method of claim 109, wherein said diverse population of stochastically generated polynucleotide sequences are produced by stochastic copolymerization of double stranded oligonucleotides.--

--115. (New) The method of claim 109, wherein said diverse population of stochastically generated polynucleotide sequences are produced by copolymerization of the four kinds of nucleotide triphosphates consisting of A, C, G and T.--

--116. (New) The method of claim 109, wherein said diverse population of stochastically generated polynucleotide sequences are produced by chemical synthesis.--

--~~117~~. 39 (New) The method of claim ~~109~~ 34, further comprising introducing said diverse population of vectors containing stochastically generated polynucleotide sequences into host cells.--

Sub C8

--118. (New) The method of claim 109, wherein step (b) further comprises digesting the diverse population of expression vectors with a restriction enzyme absent from the expression vector and reinserting the digested products into said digested population of vectors to form a new different population having a greater number of new stochastic polynucleotide sequences.--

--119. (New) The diverse population of vectors containing stochastically generated polynucleotide sequences encoding said diverse population of peptides, polypeptides, or proteins produced by the method of claim 109.--

REMARKS

Claims 1-7, 9-17, 23-26, 32-35, 40-44, 57-58, and 65-74 are pending in the present application. All claims have been canceled without prejudice and new claims 75-119 substituted therefore. Applicants reserve the right to prosecute these cancelled claims at a later time or in a later filed continuation application. The newly substituted claims raise substantive new issues of patentability and, as such, a first office action made final would not be appropriate. For example, new claim 75, is now directed to identifying a peptide polypeptide or protein having a predetermined binding property. Additionally, steps (a) and (b) have been added in new claim 75. These steps are directed to providing a ligand for the detection of the predetermined binding property and to synthesizing a diverse population of stochastic polynucleotide sequences which encodes a predetermined frequency of two or more amino acid residues at

four or more amino acid positions. New steps (a) and (b) can additionally be found in new independent claims 90 and 99 and new step (b) can be found in independent claim 109.

Support for these amendments can be found throughout the specification. More specifically, support for the amendment to "predetermined binding property" and to "ligand" can be found on page 5, lines 20-21, page 6, lines 20-23, and page 20, lines 5-9. Support for the amendment to "stochastically generated polynucleotide sequence" can be found throughout the specification and particularly on pages 10-18. Support for the use of the term "predetermined frequency" is similarly found throughout the specification and on page 1, lines 17-18, page 2, line 20 through page 4, line 8, and on pages 10-18. For example, the stochastic copolymerization of each of the four nucleotide triphosphates results in a predetermined frequency of possible amino acid residues which can be incorporated at a particular amino acid position that is equal to the degeneracy of the genetic code (page 2, lines 21-23). Similarly, stochastic copolymerization of double stranded oligonucleotides results in a predetermined frequency which assures a balanced representation of triplets specifying all amino acids at a particular amino acid position (page 12, lines 19-20). Support for chemical synthesis of stochastic polynucleotides can be found on page 18, line 5. Support for the use of the term "inserting" can be found on page 28, lines 8-9, page 2, line 23 through page 3, line 2, and page 2, lines 6-7. Support for the number of amino acid positions can be found on pages 10-18 and particularly on pages 1, 4, 12, 16 and 17 when library size and complexity are discussed because these sizes inherently disclose populations having a

predetermined frequency of two or more amino acid residues at four or more amino acid positions. For example, a library of about 10,000 completely new proteins (page 1, line 8) can be comprised of four amino acid positions having all twenty amino acid residues balancedly represented at each position. The remaining terms used in new claims 75-119 can similarly be found throughout the specification or in old claims 1-74. The amendments do not raise an issue of new matter and entry thereof is respectfully requested.

The present invention provides methods for producing DNA, RNA, peptides, polypeptides and proteins having predetermined binding properties. The methods consist of synthesizing diverse populations of stochastic nucleotide or amino acid sequences or fragments thereof, and screening the population for a desirable property or activity. Desirable properties or activities can include, for example, binding, structural, enzymatic, catalytic, antigenic, and pharmacologic. The methods rely on synthesizing a sufficiently large population, or a population with sufficient diversity so as to contain a likely probability that the sequence exhibiting, or encoding, the predetermined property is represented within the stochastic population. Identification and isolation of the DNA, RNA, peptide, polypeptide or protein can be achieved by screening the diverse population using a variety of methods known to one skilled in the art. The claimed methods utilizing large populations of stochastic sequences provide advantages over previous methods in that no prior information regarding the sequence is required. Instead, sequences encoding predetermined properties such as binding to a desired ligand can be identified

by screening the population with a detectable ligand. Applicants traverse all grounds for rejecting the claims in the final Office Action issued in connection with the parent application for the reasons which follow.

REJECTIONS UNDER 35 U.S.C. § 101

Claims 1-7, 9-17, 23-26, 32-35, 40-44, 57, 58 and 65-69 stand rejected under 35 U.S.C. § 101 allegedly because the invention lacks operable utility and is of such a nature as to constitute a mental idea or concept. In this regard, the Office Action states that the claimed process consists of searching for peptides and proteins of interests from among an infinite number of possible peptides and proteins. To be operable, the Office Action alleges that the critical step of screening and selection of peptides and proteins would have to function with a reasonable degree of certainty and the disclosure does not explain how to select peptides of interest from the vast set of all possible peptides.

The claims now under consideration are directed to methods of identifying a peptide, polypeptide or protein having a predetermined binding property. To identify such a peptide, polypeptide or protein, the claimed methods require the synthesis of a diverse population of stochastically generated polynucleotide sequences which encode a predetermined frequency of two or more amino acid residues at four or more amino acid positions. Synthesis can be achieved by, for example, random copolymerization of double stranded oligonucleotides, random copolymerization of each of the four nucleotide triphosphates or

chemical synthesis. Thus, the diverse populations are not infinite, but are as large as the stochastic synthesis methods above or other methods known in the art will practically allow. It is important to note that the operability of the claimed methods is not whether the diverse population is large or small, only that it is large enough to contain a sufficient number of different sequences such that the probability of one sequence within that population having the binding property of interest is represented with a reasonable degree of certainty. The stochastic synthesis methods described above achieve this requirement.

In regard to the assertion that the disclosure does not explain how to select peptides of interest from a vast set of all possible peptides, Applicants contend that the screening methods for identifying the peptide, polypeptide or protein of interest is not technically problematic and is not an issue for the methods of the invention to be practiced as claimed. The disclosure sufficiently describes methods for one skilled in the art to screen diverse populations of peptide, polypeptide or proteins (page 18, line 37). Moreover, various screening methods for detecting binding of a ligand to a peptide, polypeptide or protein were known to those skilled in the art.

At the time the invention was made, screening libraries for a particular binding characteristic was routine to those skilled in the art as exemplified in the art of DNA cloning. For example, DNA libraries containing greater than one million recombinants of genetically encoded information could be screened by probing plaque lifts with antibodies or nucleic acid probes.

Thus, the critical step for operability does not rely on methods for screening and selecting peptides which bind, for example, to a predetermined ligand. Applicants maintain that the invention is operable and useful as described in the specification and presently claimed. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be removed.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2-7, 9, 11, 23-26, 32-35, 41-44, 57, 58 and 65-69 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. As indicated above, Applicants have canceled claims 1-7, 9-17, 23-26, 32-35, 40-44, 57, 58 and 65-74 without prejudice and substituted new claims 75-119 therefor. In light of these new claims, Applicants believe that this grounds of rejection is moot and respectfully request its withdrawal.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST AND SECOND PARAGRAPHS

The specification is objected to and claims 1-7, 9-17, 23-26, 32-35, 40-44, 57, 58 and 65-69 stand rejected under 35 U.S.C. § 112, first and second paragraphs for allegedly failing to adequately describe or enable one skilled in the art to practice the invention as claimed. The Office Action cites various terms as allegedly lacking full, clear, and precise definition so as to be considered vague and indefinite. Many of the terms include the word "stochastic". The Office Action cites

the dictionary definition of this word as "relating to conjecture or involving random variables, probability or chance" and asserts that this definition highlights the indefiniteness of these claims. Furthermore, the term "synthetic" is not understood as distinguishing one product from another allegedly because once made, such products are indistinguishable. Finally, the Office Action alleges that the specification sheds no light on what is meant by the terms "novel fragments" and "extracellular amplification".

Applicants' amended set of claims are now directed to methods for identifying a peptide, polypeptide or protein having a predetermined binding property. The molecule having the binding property of interest is identified by screening a diverse population of peptide, polypeptide or proteins with a ligand and detecting a binding event between the ligand and a peptide, polypeptide or protein within the screened population. Choice of ligand is based on interest or need and inherently determines the sought after binding activity. Applicants believe that the amended set of claims are clear and concise to allow those skilled in the art to practice the invention as claimed.

However, to the extent that the terms objected to appear in the presently amended set of claims, Applicants set forth below the descriptions found within the specification which sufficiently enables those skilled in the art to practice the invention as now claimed. For example, included within the definition of the term "stochastic" is random. As is known to those skilled in the art, this term means that claimed populations are diverse. Diversity is an inherent outcome of the

random polymerization of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined or specific sequence. In turn, the greater diversity which can be achieved, the greater number of different sequences will be represented within the population and the higher likelihood that a particular sequence will have a particular binding activity.

The methods described and claimed in the present application achieve a sequence diversity greater than what had previously been known in the art at the time the invention was made because the sequences are stochastically synthesized. Such populations are diverse enough, or can be made diverse enough to contain at least one peptide, polypeptide or protein exhibiting the binding activity of interest. Thus, the term "stochastically generated polynucleotide sequences" as now claimed more clearly defines how the diverse populations are made and include, for example, "copolymerization of double stranded oligonucleotides"; "copolymerization of the four kinds of nucleotide triphosphates consisting of A, C G, and T"; and "chemical synthesis." Specific examples of these synthesis procedures have been described above.

To the extent the previous rejection over the use of the term "predetermined property" applies to the term "predetermined binding property" as presently claimed, Applicants point to the citations of support for this term in the beginning of the section entitled "Remarks". This term is believed to sufficiently enable one skilled in the art to practice the invention as claimed.

In light of the above remarks, Applicants believe that the claims, as amended, are sufficiently clear to enable one skilled in the art to practice the invention as claimed. Accordingly, Applicants respectively request that the rejection of claims 1-7, 9-17, 23-26, 32-35, 40-44, 57, 58 and 65-69 under 35 U.S.C. § 112, first and second paragraphs be withdrawn.

Claim 66 remains rejected under 35 U.S.C. § 112, first and second paragraphs as allegedly indefinite and failing to enable one skilled in the art to make and use the invention as claimed. In light of Applicant's cancellation of this claim, this grounds of rejection is moot and is respectfully requested to be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The specification remains objected to and claims 1-7, 9-17, 23-26, 32-35, 40-44, 57, 58 and 65-69 stand rejected under 35 U.S.C. § 112, first paragraphs as allegedly failing to provide a full written description and enablement for practicing the claimed invention. The Office Action alleges that the experimental procedures appear to be inherently inoperable and that intellectual exercises are presented instead of working examples. Briefly, the Office Action states that (1) Applicant fails to demonstrate that any new protein was made, screened or selected and isolated; (2) no workable selection scheme has been described which would enable one skilled in the art to isolate new peptides having predetermined properties without undue experimentation; (3) that there is no rational reason to look for a viral peptide to make a vaccine when success would be greater

when starting with a viral preparation; (4) the processes are limited in randomness by the introduction of bias against stop codons, for example, and that many of the processes are rerandomized in such a way as to get back the original random assembly; (5) the discussion of protein condensation appears to be inoperable and incomprehensible and (6) there appears to be no effective reduction to practice.

For the reasons stated previously in regard to the similar rejection under 35 U.S.C. § 101, Applicants maintain that the invention is operable as now claimed. To the extent that the rejections now apply to the specific experimental procedures referenced, Applicants point out that such issues have been responded to previously and no factual evidence has been put forth to refute the operability of Applicants choice of transformation volumes, and heat shock times and temperature. Applicants will now respond to each of points set forth above by indicating the appropriate number.

(1) For the reasons previously of record, Applicants maintain that the specification provides a sufficient written description which teaches those skilled in the art how to make and use the invention as now claimed. As stated previously, methods to express and screen populations of polynucleotide sequences were known to those skilled in the art. However, the use of diverse populations of stochastically generated polynucleotide sequences encoding two or more amino acids at four or more positions as a starting material to express and screen were not contemplated at the time the invention was made. Applicants have described the synthesis of polynucleotides where

all twenty amino acid residues are encoded at each amino acid position within each peptide, polypeptide or protein of the population (pages 10-18). Moreover, Applicants have previously submitted a Declaration by Dr. Kauffman which provides factual data showing the synthesis, screening and identification of a diverse population of peptide, polypeptide or proteins as now claimed. The proteins were shown to be new by (a) partial or complete loss of enzymatic activity, (b) increase in size of the protein and (c) binding to an antibody ligand.

During the prosecution of this application, Applicants have maintained that the specification teaches those skilled in the art how to synthesize the populations of peptide, polypeptide or proteins as now claimed and screen by methods known in the art to identify a predetermined binding activity. To evidence these assertions, Applicants refer to the references submitted with the Response filed February 12, 1992, and of record. Each of these references, and particularly that of Devlin et al., Cwirla et al., and Scott and Smith all show the synthesis of a diverse population of stochastically generated polynucleotide sequences which were synthesized by the copolymerization of the four kinds of nucleotide triphosphates consisting of A, C, G and T. The diverse population of peptides synthesized encoded two or more amino acid residues at four or more amino acid positions and when screened for predetermined binding activity were useful for identifying (1) streptavidin-binding peptide sequences (Devlin et al.), (2) β-endorphin antibody binding peptide sequences (Cwirla et al.) and (3) myohemerythrin antibody binding peptide sequences (Scott and Smith).

In each of these reference the authors attest to the usefulness of screening stochastic populations of peptides. For example, Devlin et al. in the abstract states

> "Libraries of random peptide sequences were constructed and screened to identify peptides that specifically bind to proteins" and "This type of library makes it possible to identify peptides that bind to proteins that have no previously known affinity for peptides".

Similarly, Cwirla et al. state at the end of the first paragraph

> "Our study shows that randomly generated peptide sequences are a rich source of ligands".

Further, Scott and Smith state

> "The value of the epitope library is that a large and important part of the epitope universe can be encompassed in a few microliters of solution and effectively surveyed for specific affinity for an antibody, receptor, or other binding protein by simple recombinant DNA methods" (last paragraph).

Thus, using methods as described and claimed in the present application, each of these publications independently corroborate Applicants assertion that the operability and utility of the claimed methods were enabled at the time the invention was made. The isolation of peptide, polypeptide or proteins by such claimed methods therefore does not require undue experimentation.

(3) Applicants provide a description in the specification for identifying peptides that are useful for the preparation of vaccines. Those skilled in the art are aware of the possible applications for identifying such vaccine sequences and include, for example, the likely situation where the viral antigen is not known but patient serum is available or purified viral preparations are unavailable or are a serious health hazard to the technician. Such reasons are further exemplified by the publications described above.

(4) The Office Action asserts that the processes are limited in randomness by the introduction of bias against stop codons. This statement is incorrect for the invention as presently claimed since the introduction of stop codons would decrease the number of possible amino acid residues that could be incorporated at a particular position to zero. Therefore, the opposite is true wherein bias toward stop codons limit randomness which is not what Applicants claim.

(5) The discussion regarding protein condensation appears to be moot in light of Applicants amendments to the claims.

(6) Applicants contend that the assertion regarding no effective reduction to practice has been effectively responded to above in Applicants response to the rejections under 35 U.S.C. § 101 and above under 35 U.S.C. § 112, first paragraph. Specifically, the methods are operable as claimed.

Claims 1-7, 9-17, 23-26, 32-35, 40-44, 57-58 and 65-69 also stand rejected under 35 U.S.C. § 112, first paragraph allegedly because the disclosure is enabling only for claims limited to a process for making β-galactosidase. The methods as now claimed are directed to identifying or isolating a peptide, polypeptide or protein having a predetermined binding property. Support for the identification of a predetermined binding property has been set forth above. Moreover, such methods were well known in the art at the time the invention was made. In light of these amendments, the description and what was known in the art, Applicants believe that the methods are enabled as now claimed.

Claims 70-74 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly involving new matter. This rejection is moot in light of the cancellation of these claims.

In light of the amendments and the above remarks, it is believed that all rejections under 35 U.S.C. § 112, first paragraph, are overcome and should be withdrawn.

PRIOR ART REJECTIONS

Claims 1-7, 9-17, 23-26, 32-35, 40-44, 57-58 and 65-68 remain rejected under 35 U.S.C. § 102 (e) as allegedly anticipated by Sirotkin. Claim 65 remains rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Fox et al., Milkman et al., Ohno, Houghten, or Geysen et al. Claim 69 remains rejected under 35 U.S.C. § 102 (b) as allegedly

anticipated by or, in the alternative, under 35 U.S.C. § 103 as allegedly obvious over Maniatis et al. or Grundstrom et al. Claims 1-7, 9-17, 23-26, 32-35, 40-44, 57-58 and 65-68 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Riggs taken with Matteucci et al., Traboni et al., and Joyce, and further in view of Fox et al.

Applicants cancellation of the above claims and substitution of new claims is believed to render these rejections moot. None of the cited references either alone, or in combination, teach or suggest a method of identifying a peptide, polypeptide or protein having a predetermined binding property wherein a diverse population of stochastically generated polynucleotide sequences are synthesized where each sequence within the population encode two or more amino acid residues at four or more amino acid positions. Similarly, none of the cited references, either alone or in combination, teach or suggest screening such a population of expressed stochastically generated polynucleotide sequences with a ligand to identify a predetermined binding property. Applicants therefore respectfully request withdrawal of this grounds of rejection.

CONCLUSION

In light of the foregoing amendments and remarks, Applicants respectfully request withdrawal of all rejections and solicit an allowance of the pending claims. The Examiner is

invited to contact Cathryn Campbell or the undersigned agent at (619) 535-9001 if there are any remaining issues to be resolved.

Respectfully submitted,

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